04-13-01

JC Rec'd PCT/PTO 12 APR 2001 PCT

FORM PTO-1390 (Modified) (REV 10-95) U.S. DEPAR .T OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

A RNEY'S DOCKET NUMBER	
P-6191	
U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR	
09/807586	
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE
PCT/IB99/01670	13 October 1999
PRIORITY DATE CLAIMED	
14 October 1998	

TITLE OF INVENTION
TAXOL/CISPLATINUM PREPARATION PACKAGING

APPLICANT(S) FOR DO/EO/US
Rolland-Yves MAUVERNAY

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ A copy of the International Search Report (PCT/ISA/210).
8. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 18 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
    A **SECOND** or **SUBSEQUENT** preliminary amendment.
16. ☐ A substitute specification.
17. ☐ A change of power of attorney and/or address letter.
18. ☒ Certificate of Mailing by Express Mail
19. ☒ Other items or information:

Cover Page of published PCT International Application No. PCT/IB99/01670
Verification of English Translation of International Application
Translation of amended Specification, page 2 and claims pages 9 and 10
Substitute Drawing Sheet numbers 1 through 6, containing Figures 1-7
Return Receipt Postcard

PCTUS1/REV03

JC03 Rec'd PCT/PTO 12 APR 2001

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/807586	PCT/FR98/01037	P-5639

20. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

- ☒ Search Report has been prepared by the EPO or JPO $860.00
- ☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) . . . . . .
- ☐ No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) . . . . . .
- ☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO . . . . . .
- ☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) . . . . . .

	CALCULATIONS PTO USE ONLY	
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$860.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	9 - 20 =	0	x $18.00	**$0.00**	
Independent claims	1 - 3 =	0	x $80.00	**$0.00**	
Multiple Dependent Claims (**check if applicable**).			☒	**$270.00**	
TOTAL OF ABOVE CALCULATIONS			=	**$860.00**	
Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) (**check if applicable**).			☐	**$0.00**	
SUBTOTAL			=	**$1,130.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).			+	**$0.00**	
TOTAL NATIONAL FEE			=	**$1,130.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (**check if applicable**).			☐	**$0.00**	
TOTAL FEES ENCLOSED			=	**$1,130.00**	
				Amount to be: refunded	$
				charged	$

☐ A check in the amount of to cover the above fees is enclosed.

☒ Please charge my Deposit Account No. **18-2284** in the amount of **$1,130.00** to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **18-2284** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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34,639
REGISTRATION NUMBER

April 12, 2001
DATE

Oxaliplatinum preparation packaging

The invention concerns a pharmaceutical preparation of oxaliplatinum packaged in a container, preferably in a sealed soft (flexible) bag for medical use.

The optically active complex of platinum, cis-oxalato(trans-*l*-1,2-diaminocyclohexane)platinum(II), under its international nonproprietary name (INN) "oxaliplatinum", is known to possess anti-tumour properties and its preparation was described in the patent US 4,169,846.

Oxaliplatinum, like other platinum complexes such as Cisplatin or Carboplatin, is used as an antineoplastic, cytostatic agent for the therapeutic treatment of various types of cancer. These include, *inter alia*, cancer of the colon, ovaries, upper respiratory passages or epidermal (skin) cancers as well as germ cell tumours (testes, mediastinum [interpleural space], pineal gland etc.). The use of oxaliplatinum is particularly appropriate for the treatment of colon cancers that are resistant to pyrimidines, of small cell lung cancers, non-Hodgkin lymphomas, breast cancers, cancers of the upper respiratory-digestive passages, malignant melanomas, liver carcinomas, uro-epithelial cancers, cancers of the prostate etc.

International Patent Application WO 96/04904 describes a pharmaceutical preparation of oxaliplatinum in aqueous solution. This preparation has the advantage of obtaining a ready-to-use, injectable solution of oxaliplatinum that is simpler and more reliable in use and less expensive to manufacture than a preparation starting with a lyophilisate (freeze-dried substance). It has a chemical purity (no racemisation) and therapeutic activity equivalent to or greater than those obtained by starting with a reconstituted lyophilisate.

This pharmaceutical preparation was stored in bottles made of neutral glass for pharmaceutical use under an inert gas atmosphere. However, such bottle packages, although appropriate for long-term storage of the pharmaceutical preparation, are unsuitable for containing this preparation during administration by perfusion.

Flexible bags consisting of a material based on polyvinylchloride (PVC) are used during perfusion procedures of liquid preparations of platinum complexes other than oxaliplatinum, such as cisplatin or carboplatin.

However, and in contrast to what has been observed for liquid preparations of cisplatin and carboplatin, it has been found that particularly because of their greater chemical sensitivity, pharmaceutical preparations of oxaliplatinum in aqueous solution cannot tolerate being in contact with PVC-based materials, nor can they be transported and/or stored in containers, especially flexible bags, based on these materials.

The aim of the present invention is to provide liquid pharmaceutical preparations of oxaliplatinum that can not only be stored for a long period of time without any detectable loss of quality but can also be used in particular for perfusion procedures without any need for the nursing personnel to perform an operation to decant liquid pharmaceutical preparations.

For this purpose, the present invention concerns a leakproof (impervious) flexible bag for medical use containing a pharmaceutical preparation of oxaliplatinum in liquid form as defined in Claim 1. The various embodiments are as defined in Claims 2 to 9.

The invention will be set out below with the help of the Drawings in which

- Fig. 1 shows a cross-sectional view of the envelope of the flexible bag used in the invention;
- Fig. 2 shows a cross-sectional view of the flexible bag used in the invention;
- Fig. 3 shows a comparison graph of the liquid phase water permeability firstly of PVC and secondly of a suitable construction material for the envelope of the flexible bag used in the invention, before and after a sterilisation procedure;
- Fig. 4 shows a comparison graph of the vapour phase water permeability of various suitable construction materials for the envelope of the flexible bag used in the invention, before and after a sterilisation procedure;
- Fig. 5 shows a comparison graph of the oxygen permeability of various suitable construction materials for the envelope of the flexible bag used in the invention, before and after a sterilisation procedure;
- Fig. 6 shows the pH variation over time of a preparation according to the invention; and
- Fig. 7 shows the pH variation over time of a liquid pharmaceutical solution of oxaliplatinum stored in a glass bottle under an inert gas atmosphere.

The pharmaceutical preparation of oxaliplatinum according to the present invention is stored, then used directly, in a flexible bag constructed from plastics materials chosen from among polyethylenes (PE), polypropylenes (PP), polyethyl and polyvinyl acetates, polyamides (PA) and polyisobutyls (PIB). Latex (rubber) can also be used.

As shown in Fig 1, the envelope of the bag preferably has a multi-layer structure. More preferably, the internal layer in direct contact with the pharmaceutical preparation consists of PP and the external layer or possible intermediate layers can consist of any of the above-mentioned plastics. The external layer or the possible intermediate layers can even consist of PVC, the oxaliplatinum not being in direct contact with this material.

As shown in Fig. 2 and according to a particular embodiment of the invention, the flexible bag can consist of welded sheets of multi-layer materials. Preferably the flexible bag can consist of at least two sheets welded together. More preferably, this bag can consist of two welded sheets of multi-layer sheet materials comprising one film of 11-amino-undecanoic acid (PA 11) bonded by at least one of its surfaces to a film of PP by the use of a polyolefine film, the PP films forming the internal wall of the leakproof flexible bag.

The flexible bag of the invention preferably consists of a material comprising 70 % of PP and 30 % of PA 11 and commonly called V90.

Astonishingly it has been found, during a physico-chemical study performed before and after the sterilisation procedure and comparing the liquid phase water permeability properties of flexible bag envelopes consisting firstly of PVC and secondly of V90, that the bags based on V90 material constitute an excellent barrier to water loss generally due to evaporation. This property is not found in the classical PVC bags, not even those using PVC as a constituent of the inner layer.

The results of this study are shown diagrammatically by the graph of Figure 3.

During a second study comparing the vapour phase water permeability properties of PVC and various construction materials for the flexible bags used in the invention, the material V90 proved to be the most leak-tight (impervious) as shown by the diagram in Fig. 4.

Such properties of imperviousness to water in its two forms, liquid and vapour, are extremely important when contemplating the use of such a material for the construction of the flexible bags used for the invention. In fact, the almost zero losses of water guarantee the maintenance of an almost constant concentration of the pharmaceutical preparations of oxaliplatinum over time. Excessive packaging of the envelope of the bag used for the invention is thus unnecessary.

The impermeability to oxygen of the V90 material was also studied and compared to that of PVC, and proved to be at a far superior level. The results of this comparative study are shown diagrammatically in Fig. 5.

This property of impermeability to oxygen is very important in view of the sensitivity of oxaliplatinum to oxidising substances, the degradation products generated during such oxidation generally being inactive from the pharmacological point of view and may even be toxic to the organism. This property is very suitable during the use of the flexible bag, which has the advantage compared to glass bottles of not needing the presence of an inert gas atmosphere.

The V90 material also affords the advantage from the ecological point of view of being recyclable and reusable in another form, which is not the case with PVC.

Another attractive aspect of the use of the aforementioned materials, particularly PP (V90), lies in the ability to make leak-tight welds very easily. In this way it is possible to obtain flat compartmented bags. This property is not achievable with a PVC material, which requires the use of connectors to communicate between the various compartments. Unfortunately these connectors are a source of leaks, which is not observed in the case of bags made of PP (V90).

These compartments can be multiple so as to allow the mixing of different solutions. These compartments can contain the solution already ready for use, at the right dose, and can be withdrawn or used directly by the medical personnel without the risk of error.

The aforesaid materials, particularly PP (V90), also have the advantage of withstanding high temperatures better. This is particularly attractive during the sterilisation of flexible bags containing a solution of oxaliplatinum by autoclave. This sterilisation is much simpler because the exposure time can be reduced by increasing the temperature.

The liquid oxaliplatinum solution contained in the bags preferably has a concentration between 1 and 8 mg/ml. According to one particular embodiment of the invention, the oxaliplatinum concentration lies between 1 and 5 mg/ml at a pH between 4 and 7, ideally between 4.5 and 6.0.

According to one particular embodiment of the invention, the concentration of oxaliplatinum in the preparation contains at least 95 % of the initial concentration and has a clear, colourless appearance free from precipitate after storage during a pharmaceutically acceptable period.

A test of the stability of the liquid solution of oxaliplatinum (Tanaka K.K., Batch LO 92 TO 34) was carried out. To do this, 100 ml bags consisting of PA 11/PP 60/140 and measuring 13.0 x 12.5 cm were used. The bags contained 200 mg of oxaliplatinum at a concentration of 2 mg/ml, i.e. 100 ml of liquid oxaliplatinum solution per bag. This test was performed over a total of 12 weeks in accordance with the sampling plan shown in Figure 8. The bags were subjected to what are called accelerated storage conditions at a temperature of 40° C and a relative humidity (RH) of 75 %.

The results of this accelerated stability study are summarised in Table 1

Kinetic parameters	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 12	6 Months	12 Months
Appearance of the solution	Clear, colourless	Clear, colourless	Clear, colourless	Clear, colourless	Clear, colourless	Clear, colourless	Clear, colourless	Clear, colourless	Clear, colourless
L-OHP titre/ standard (%)	99.7	100.1	100.0	100.9	99.3	97.7	99.3	98.9	98.5
Oxalic acid titre (%)	< 0.1 %	< 0.1 %	< 0.1 %	< 0.1 %	< 0.1 %	< 0.1 %	< 0.1 %	< 0.1 %	< 0.1 %
Visible impurities (%)	0.10	0.60	0.50	0.50	0.48	0.45	0.40	0.5	0.6
pH	5.56	5.10	5.24	5.22	NM	5.23	5.35	5.20	5.30

NM = Not measured

In a surprising manner, the liquid solution of oxaliplatinum packed in a flexible bag is stable for a period extending to more than three months, and even to more than six months.

Astonishingly, this liquid solution of oxaliplatinum packed in a flexible bag appears to remain stable for at least one year.

The appearance of the solution was observed for twelve months, and to our great astonishment showed clarity and the absence of coloration over the whole of this period. Analysis of the concentrations was performed by high pressure liquid chromatography (HPLC = High Performance Liquid Chromatography).

As far as the concentration of oxaliplatinum is concerned, a stated quantity lying between 95 and 105 % was obtained, taking into account the limit of resolution of the system. As far as the determination of oxalic acid is concerned, the maximum limit is 0.5 % by the HPLC method.

The maximum percentage of apparent impurities determined in the same way was 2 %.

Fig. 6 shows the development of the pH over 12 weeks. This pH lies between 4.7 and 5.9, and varies very little with time, which is good proof that the oxaliplatinum solution remains stable in this type of bag. This system shows a stability analogous to that observed for a solution of oxaliplatinum subjected to the same conditions and packed in a glass bottle, as Fig. 7 shows.

All of the above results show consistently that pharmaceutical preparations of oxaliplatinum can be stored in flexible bags for a long period without any chemical degradation of the oxaliplatinum being observed, from the moment they are no longer in direct contact with PVC-based material. Because of the flexibility of the materials of which the bags consist, such preparations are ready to be used for transfusion procedures without any decanting operation being necessary.

Claims

1) Flexible impervious bag for medical use containing a pharmaceutical preparation of oxaliplatinum in liquid form, wherein said flexible bag is constructed from plastic material, excluding, for the said material in direct contact with the said pharmaceutical preparation, PVC-based material.

2) Flexible impervious bag for medical use containing a pharmaceutical preparation of oxaliplatinum according to Claim 1, wherein the envelope of said bag has a multi-layer structure.

3) Flexible impervious bag for medical use containing a pharmaceutical preparation of oxaliplatinum according to one of the foregoing Claims, wherein the liquid solution of oxaliplatinum is in contact with an internal layer of the said envelope consisting of a polypropylene material.

4) Flexible impervious bag for medical use containing a pharmaceutical preparation of oxaliplatinum according to one of the foregoing Claims, wherein the concentration of oxaliplatinum in the pharmaceutical preparation is between 1 and 8 mg/ml.

5) Flexible impervious bag for medical use containing a pharmaceutical preparation of oxaliplatinum according to Claim 4, wherein said concentration is between 1 and 5 mg/ml.

6) Flexible impervious bag for medical use containing a pharmaceutical preparation of oxaliplatinum according to one of the foregoing Claims, wherein said flexible bag consists of two welded sheets of multi-layer sheet material comprising one film of polyamide of 11-amino-undecanoic acid bonded by at least one of its surfaces to a film of polypropylene by means of a film of polyolefine, the polypropylene films forming the internal wall of the watertight flexible bag.

AMENDED PAGE

7) Flexible impervious bag for medical use containing a pharmaceutical preparation of oxaliplatinum according to one of the foregoing Claims, wherein said flexible bag is multi-compartmented.

8) Flexible impervious bag for medical use containing a pharmaceutical preparation of oxaliplatinum according to Claim 7, wherein the multi-compartments are defined in such a way as to allow the dosing of a ready-for-use preparation.

9) Flexible impervious bag for medical use containing a pharmaceutical preparation of oxaliplatinum according to one of the foregoing Claims, wherein said solution has a pH of 4.5 to 6.0, a concentration of oxaliplatinum in the preparation of at least 95 % of the initial concentration, as well as a clear, colourless appearance free from precipitate after storage for a pharmaceutically acceptable period.

Docket No.

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

OXALIPLATINIUM PREPARATION PACKAGING

the specification of which

(check one)

- ☐ is attached hereto.
- ☐ was filed on _____ as United States Application No. or PCT International Application Number PCT/IB99/01670 and was amended on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority ~~Not~~ Claimed
2067/98	SWITZERLAND	14/10/1998	☒
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country)	(Day/Month/Year Filed)	

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112. I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
PCT/IB/99/01670	October 13, 1999	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

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